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TITLE: Effect of Teriparatide, Vibration and the Combination on Bone Mass and Bone Architecture in Chronic Spinal Cord Injury

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Severe bone loss commonly occurs in individuals with chronic spinal cord injury who are non-weight-bearing and leads to an increased risk of lower extremity fractures. This 12 month, multi-site, double-blind, randomized, placebo-controlled study evaluates the efficacy and safety of two interventions known to be anabolic to bone, parathyroid hormone and mechanical loading (provided as teriparatide and vibration, respectively) in 60 SCI individuals with low bone mass. At the end of the fourth year of this project, enrollment has been completed. 56 out of 60 participants completed year 1 of the study (retention rate of 93%); 25 participants who completed elected to begin a one year open-label extension of teriparatide therapy. No safety issues have arisen during the course of the study. Data from the first year of study are being finalized, and results regarding efficacy will only be available after database lock and subsequent analysis.

15. SUBJECT TERMS
Spinal cord injury, bone density, osteoporosis, teriparatide, vibration

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INTRODUCTION:

After acute spinal cord injury (SCI), individuals unable to ambulate experience rapid and profound bone loss of as much as 50% in their lower extremities over the ensuing 2-5 years. This bone loss results in their having a significantly increased risk of fracture thereafter. This study evaluates the ability of two interventions, parathyroid hormone and mechanical loading, separately and together, to increase bone mass and improve bone quality in individuals with chronic SCI and low bone mass. These interventions have previously been shown to be effective in increasing bone mass and decreasing fractures in non-disabled populations of men and post-menopausal women but not examined in individuals with SCI. In this three-arm, modified factorial design, double-blind, placebo-controlled study, 60 people with chronic SCI will receive daily teriparatide and mechanical vibration. Assessment of bone mass (by DXA scanning and quantitative computed tomography), bone quality (by finite element modeling), and bone metabolism (by serum bone markers) will be undertaken at baseline and at regular intervals during one year of treatment to permit evaluation of the efficacy of these interventions.

BODY:

Overview of Yr4 Progress:

During the fourth year of this program, the focus has been on completion of study visits and data collection. Recruitment was successfully completed in August, 2013, with a total of 50 participants having been enrolled at the Northwestern/RIC site and 11 at the Edward J. Hines, Jr. VA site (see attachment). All study visits for the initial trial have been completed at both sites and all data have been collected. The last study visit took place on August 9, 2014.

At the end of year 4, 56 participants completed the original protocol (45 enrolled at Northwestern/RIC and 11 at the VA; see attachment). Retention of study participants was excellent with only 4 out of 60 (7%) having withdrawn and not available for follow-up.

Data from all participants who have completed the first year of the study continues to be entered into the study database at both sites. Serum samples for bone biomarkers from all participants who completed the original study will be sent for batch analysis testing to Maine Medical Center Research Institute.

Regulatory approvals at all sites are up to date. In the last year, University of Illinois at Chicago where the CT analyses were taken place was closed as a site. These analyses were being done primarily by Dr. W. Brent Edwards, who has taken a position as Assistant Professor at the University of Calgary. The Northwestern University/RIC, Edward Hines, Jr. VA IRBs, and USAMRMC HRPO have all approved the addition of Calgary as a site for CT analysis. CT scans for the original study have been sent to Calgary and CT analyses are up to date.

Because teriparatide treatment continues to be anabolic for more than a single year, we requested to be able to extend treatment for a second year for those participants who wished to do so upon completion of the original protocol. An extension protocol was approved by USAMRMC HRPO and participants are being enrolled and treated with data collection continuing. The existing IND has been updated with this additional information. The one year teriparatide extension component of the current study is taking place at Northwestern University/RIC and the University of Calgary; the Edward Hines, Jr.

VA will not be participating in the extension. Regulatory approval for all sites has been obtained for the extension study at all of the local ethics committees and USAMRMC HRPO.

Participant recruitment for the one year teriparatide extension study has been completed in August 2014. 25 subjects have been enrolled at Northwestern University/RIC. Out of the 25 enrolled participants, 12 (48%) participants have completed the extension arm, and 13 (52%) remain active. The last study visit is anticipated for August 2015.

Treatment has been well tolerated and no unexpected safety issues have been identified in either study. The Medical Monitor has reviewed the studies at 3 meetings and recommended continuation.

Research Accomplishments:

The following items are listed in the statement of work (SOW) for Yr 4 of the project. Progress and current status are listed for each:

1. Identify and recruit participants.

   Enrollment into the study has been successfully completed. The last participant was enrolled in August, 2013, for the initial study. Enrollment into the extension study was completed in August, 2014, as noted above.

2. Perform all study visits, assessments and procedures as outlined in the protocol.

   All study visits for the first year of the study have been completed. Study conduct has been excellent. Retention of participants in the study has been better than expected. Only 4 participants who had been entered into the study are no longer being followed (retention rate of 93%). 25 Participants have elected to initiate a second year of treatment and are being currently assessed.

3. Continue to collect and monitor safety data with reporting as needed to the IRB, Medical Monitor and HRPO.

   All adverse event data are being systematically collected. This is inclusive of the initial study and the extension protocols. No unanticipated serious adverse events related to the study interventions (drug or device) have been reported at this time. There have been 3 meetings in Year 4 with the medical monitor and study statistician to review the study procedures and adverse events. We continued to be especially vigilant regarding incident fractures and had a decrease in the rate compared to previous years in the study. It was felt that there was no evidence for an increased risk of fractures but this would continue to be monitored. No other potential safety concerns were identified. In all study reviews the recommendation from the medical monitor was to continue the study without changes.

4. Collect, verify and enter all data into the database.

   The research database has been updated and finalized. Data continue to be entered. A double-data entry system is being employed to assure high data accuracy. Data entry is expected to be completed for the first year of the study during the first quarter of FY05.

5. Obtain serum samples and store for batch analysis at the end of the study.

   Serum samples have been collected on all participants and are being stored for batch analysis. Plans are for samples from the initial phase of the study to be sent to Maine Medical Research Laboratories during the first quarter of FY05 for analysis.

6. Collect all DXA data and enter into database.

   All DXA data collected to date have been analyzed and entered into the study database.

7. Acquire all CT data and transmit to University of Calgary for analysis.
   CT data acquisition has been completed for the original study and is on-going for all active participants in the extension arm. Data collected from Northwestern and VA for the original study have been transferred to University of Calgary for analysis. Analysis of these data is currently on-going.

8. Meet every 6 months with Medical Monitor to review safety reports.

   Three meetings with the medical monitor occurred. An extra visit was planned, as noted above, to review whether the occurrence of fractures represented a safety concern. This was not deemed to be the case. The recommendations from the Medical Monitor have been in all instances to continue the study in its current form. No safety issues have been identified.

9. Complete annual report to IRB and regulatory authorities.

   All annual and regulatory reports have been filed and accepted.

During the past year, the scope of the SOW has been expanded to include a final year of treatment with alendronate for those individuals completing year one of the current study. This has received Northwestern IRB approval and is currently being reviewed by the USAMRMC ORP HRPO. In order to provide funding for this added year of treatment, a proposal for funding was submitted to the Joint Warfighters Medical Research Program but was not successful. Additional funding to permit conclusion of the study is currently being sought. Extension of the study to a 5th year has been requested and is under review; funds initially allocated for this study will be used for continued support to allow completion of data collection and analysis if the initial study data.

KEY RESEARCH ACCOMPLISHMENTS:

There are no outcome data available to date. As this is a blinded clinical trial, scientific data relating to study objectives will not be available until all participants have concluded the study, data cleaned and data base locked, and analyses completed.

REPORTABLE OUTCOMES:

All study visits from the initial one-year protocol have been completed. However, no data are available of the effects of the interventions being assessed as we remain blinded until the database is locked.

CONCLUSION:

This project has not progressed to the point of being able to provide any conclusions in regard to the effect of these specific interventions on bone mass or bone quality in people with spinal cord injury. Enrollment and all study visits have been completed. Data entry has also been completed with final data cleaning currently in progress. The data-base lock is expected to occur at the beginning of year 5.

REFERENCES:

None.

APPENDICES:

None.

SUPPORTING DATA:

Demographics of Enrolled Participants

Demographic Data

Mean Age (yr, SD)	45.7 ± 16.7
Sex	49M/11F
Ethnicity	48 Not Hispanic or Latino, 12 Hispanic or Latino
Race	29 White, 28 Black, 2 Native Hawaiian/Other, 1 Asian
BMI	24.9 ± 6.2

Clinical Descriptors

Time post-SCI (yr, SD)	18.9±13.8
Injury Level (cervical/thoracic/lumbar)	19 C/39 Th/ 2 L
Motor Complete/Incomplete	46 Complete/14 Incomplete

Baseline BMD Values (SD)

Spine BMD	0.991 ± 0.15
R Total Hip	0.659 ± 0.11
R Femoral Neck	0.657 ± 0.12
L Total Hip	0.630 ± 0.15
L Femoral Neck	0.637 ± 0.17

Study Status

Summary – Initial Study

	NU	VA	Total
Signed ICF	104	29	133
Screen Failure	54	18	72
Run In	n/a	n/a	n/a
Randomized	50*	11	61
Active	0	0	0
Completed Mo 12	45	11	56
Lost to Follow up	4	0	4
Enrolled Extension	25	n/a	25

* 1 participant randomized but not treated

Teriparatide Extension	
	NU
Signed ICF	25
Enrolled	25
Active	13
Completed Mo 12	12
Lost to Follow up	0